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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Srivastava et al.

Confirmation No.: 1802

Serial No.: 09/873,403

Art Unit: 1642

Filed: June 4, 2001

Examiner: Christopher H. Yaen

For: COMPLEXES OF ALPHA (2) MACROGLOBULIN AND ANTIGENIC MOLECULES FOR IMMUNOTHERAPY

Attorney Docket No: 8449-178-999

DECLARATION OF PRAMOD K. SRIVASTAVA UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, PRAMOD K. SRIVASTAVA, do declare and state that:

1. I am a citizen of India, and a permanent resident of the United States residing at 70 Pheasant Run, Avon, Connecticut 06001.

2. I am a co-inventor with Robert J. Binder of the invention described and claimed in the above-identified patent application, Application No. 09/873,403 ("the '403 application"). I am a co-founder and shareholder of Antigenics, Inc., exclusive licensee of the above-identified application.

3. I am currently Professor of Immunology and Director of the Center for Immunotherapy of Cancer and Infectious Diseases at the University of Connecticut School of Medicine, the position I have held from January 1997 to the present. The University of Connecticut Health Center is assignee of the above-identified application. From 1993 to December 1996, I was a member of the Department of Biological Sciences at Fordham University, Bronx, New York, where I served as Professor and Head of the Cancer Immunology Program.

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4. My academic and technical experience and hon rs, and a list of my publications are set forth in my curriculum vitae, which is attached hereto as Appendix 1.

5. I have read and am familiar with the '403 application. The '403 application teaches compositions comprising purified molecular complexes comprising an alpha (2) macroglobulin (α2M) polypeptide noncovalently associated with an antigenic molecule that displays the antigenicity of an infectious disease or a cancer. The '403 application discloses the use of such complexes for treatment or prevention of an infectious disease or a cancer.

6. I have read and am familiar with the pending claims and the outstanding Office Action dated November 11, 2003 for the '403 application. I have been informed and believe that the claims of the '403 application are subject to a rejection based on the contention that the '403 application does not provide sufficient guidance for how to select appropriate antigens that would be useful for treatment of disease, and that such selection of appropriate antigens would require undue experimentation. I have been informed and believe that the claims of the '403 application are subject to a rejection based on the contention that the field of preventing cancer and infectious disease such as HIV infection is unpredictable and that model systems for discovery of drugs for these purposes are also not predictive, so that undue experimentation is allegedly required to use the claimed compositions for the prevention of diseases such as cancer and HIV.

7. The following experiment was conducted by me or under my supervision at the Center for Immunotherapy of Cancer and Infectious Diseases at the University of Connecticut School of Medicine. The experiment describes the use of alpha (2) macroglobulin (α2M) complexed with an antigenic molecule that displays the antigenicity of a tumor-specific antigen (synthetic ovalbumin peptide (OVA20)), which exemplifies the compositions of the invention described in the specification. The complex was administered to mice which were subsequently challenged with tumors and tumor growth was monitored. The results demonstrate that the teachings of the '403 application are sufficient to successfully use the compositions comprising α2M-antigenic molecule complexes in a prophylactic cancer model.

8. The experiment is a tumor challenge assay in which mice were

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innoculated with α2M complexed with (OVA20), a 20-mer extended variant of the K^b-binding epitope OVA8 of OVA, and then challenged with live tumor cells transfected with OVA. In the experiment shown in Figure 1 (see Appendix 2), α2M or gp96 was complexed with synthetic OVA20 peptide. α2M-peptide compl xes were injected into mice intradermally on days -14 and -7. Mice were then challenged with live B16-F10 tumor cells transfected with OVA on day 0 and tumor growth was monitored. The fractions in the top left corner of panels A-E of Figure 1 correspond to the number of mice surviving past day 22. Groups of five mice (represented by the five lines of each graph) were used for each of the substances administered. Mice were administered either (A) phosphate buffered saline (PBS) alone, (B) α2M complexed to OVA20 with PBS as a buffer, (C) α2M with PBS as a buffer, (D) the heat shock protein gp96 complexed to OVA20 with PBS as a buffer, or (E) the heat shock protein gp96 (purified from normal liver) with PBS as a buffer. As shown in Figure 1, tumor volume increased dramatically by day 22 for all mice.

9. The results of administration of α2M complexed to OVA20 shown in Figure 1, panel B, demonstrate that tumor growth was significantly delayed or no tumor growth was observed in mice immunized with α2M-OVA20 complexes. By day 22 tumor volume did not exceed 300 mm^3 in any of the mice and all mice survived to day 22. The small amount of tumor growth observed did not appear until day 20, in contrast to the PBS control where tumor growth was observed before day 10. The measure of significance was ($P<0.05$). In panel C, the results of administration of α2M alone are shown. Only one of the five mice survived to day 22, which is the same survival number for the PBS control. All mice exhibited tumor growth which began early around day 10, similar to the PBS control. In panel D, the results of administration of the heat shock protein gp96 complexed to OVA20 show that by day 22 tumor volume did not exceed 300 mm^3 in any of the mice, indicating that tumor growth is suppressed in comparison to the PBS control. Thus, administration of the heat shock protein gp96 complexed to OVA20 is less effective at delaying the onset of tumor growth and suppressing tumor growth in comparison to administration of α2M complexed to OVA20, though tumor growth was suppressed by a significant degree ($P<0.05$). In panel E, the results of administration of gp96 alone as a control are shown. Only two of the five mice survived to day 22, which is the same survival number for the PBS control. All mice exhibited tumor growth which began early around day 10, similar to the PBS control.

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10. In summary, the experiment described above demonstrates that tumor growth was significantly delayed or no tumor growth was observed in mice immunized with α2M complexed to a tumor-specific antigenic molecule. These results also demonstrate that administration of a composition comprising α2M complexed to a tumor-specific antigenic molecule can effectively be used to prevent cancer.

11. In view of the foregoing, I conclude, and others skilled in the art would also conclude, that complexes of α2M and antigenic molecules which display the desired antigenicity of a cancer-specific or an antigen of an infectious agent can readily be used, according to the methods of the '403 application, for treating or preventing infectious disease or cancer.

12. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 3/8/04

PRAMOD K. SRIVASTAVA

Attachments:

Appendix 1: *Curriculum Vitae* of Pramod K. Srivastava

Appendix 2: Figure 1: Anti-tumor immunity elicited by alpha2M-peptide complexes

Appendix 3 Materials and methods for experiments

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